METHOD OF CONTROLLING THE FLOW IN A FLOW SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application No. 10/204,177 filed October 21, 2002, which is the National Stage of International Application No. PCT/DK01/00096 filed February 13, 2001. The entire disclosures of those prior applications are hereby incorporated herein by reference

FIELD OF THE INVENTION

The invention concerns a method of controlling the flow of a liquid in a flow system, the liquid flow comprising particles and being led into a channel thereof, and as flow system with controlled flow of such a liquid.

BACKGROUND

The sorting of biological materials in the form of cells and microorganisms is typically carried out with a flow-cytometer, which has a sorting module.

A commonly known principle for the sorting of biological materials is brought about by first converting the liquid flow into drops, after which the drops are separated electrostatically.

With another principle, use is made of a method of separation where a volume element in a liquid flow is directed via a separate channel in relation to a main flow.

Examples of the latter principle are e.g. described in US Patent No. 3827555, where the separation is effected by means of mechanical valves, which are controlled on the basis of a signal from a photo-detector. However, the problem with the use of mechanical valves is that they have a relatively poor reaction time, and moreover that they unavoidably influence the flow pattern when they are activated.

In order to alleviate this problem, in US Patent No. 4756427 it is suggested that use be made of a piezo element which, however, is a relatively expensive component.

From WO 98/10267 a flow-switch is known where, by controlling of the part of a right and a left flow, an intermediate liquid flow can be positioned in such a manner that it can be directed through several branches at the outlets. This method is intended especially for the injection of a small liquid volume.

SUMMARY OF THE INVENTION

It is now an object of the present invention to provide a method and a flow system, which results in a faster and cheaper separation of particles.

The object of the invention is achieved by a method of controlling the flow of a liquid in a flow system, the liquid flow comprising particles and being led into a channel thereof, the method comprising the steps of:

- enveloping the liquid flow by a flow of carrier liquid (2),
- hydrodynamically focussing the particles in the liquid flow,
- providing a measurement signal of the liquid flow from an observation area (4) in the channel, and
- dividing the liquid flow at a branching point (7) into two or more outlets in response to said measurement signal,
- wherein said division of the liquid comprises:
- introducing a control liquid from at least one control channel (5,6) at a merging point (30) in the channel, the amount of said control liquid being controlled by at least one electro-kinetic pump, the pump effect of

which is controlled in response to said measurement signal.

Also, the object of the invention is achieved by a flow system with controlled flow of a particle-containing liquid, the flow system comprising:

(a) a channel for leading a flow of the particle-containing liquid (1) to be controlled;

(b) a carrier-liquid enveloping means for enveloping the flow of particle-containing liquid in a carrier liquid (2) in the channel so that the particles are hydrodynamically focussed in the flow of particle-containing liquid to flow in an individual manner;

(c) an observation area (4) in the channel;

(d) a measuring equipment for providing a measurement signal of the flow of particle-containing liquid in the observation area; and

(e) a branching point (7) for dividing the flow of particle-containing liquid into two or more outlets (8,9) in response to the measurement signal;

which further comprises:

(f) a merging point (30), or merging area (31) for introducing a control liquid into the channel from at least one control channel (5,6), and

(g) at least one electro-kinetic pump (11,12,13) for controlling the amount of said control liquid from said at least one control channel; said

control of the amount of control liquid being controlled by controlling the pump effect of said at least one electro-kinetic pump in response to the measurement signal.

In this way a system is provided where no use is made of mechanical components, which furthermore makes the system suitable for disposable set-ups, e.g. for use in so-called analysis kits.

The pump control is simple, as the pump effect varies proportionally with the applied electrical field, which is adapted to suit the given characteristics of pump liquid and the dimensions of the pump channels.

It should be noted that in addition to being able to control the central particle flow by the supply of a control liquid, a control of the central particle flow could also be achieved by the electro-kinetic pumping of liquid away from the central flow, naturally providing that this liquid permits the use of electro-kinetic pumping mechanisms. Moreover, the two control methods can be combined, hereby achieving, among other things, a greater displacement of the central particle flow.

It is expedient for the method to be executed as disclosed in claim 2, in that the electro-kinetic pumps are of the electro-osmotic type and consist of two capillary structures to each of which an electrical field is applied, so that when the field in the one capillary structure is increased, the field in the other capillary structure is correspondingly reduced.

By a particularly simple embodiment of the method according to the invention, as disclosed in claim 4 this is executed by the amount of control liquid being controlled by just one electro-kinetic pump which is placed in the one of the channels. By introducing control liquid in greater or smaller degrees, or by pumping liquid away from the channel, the central particle flow can be controlled between the two outlets. The configurations with differences in the channel cross-section, as well as asymmetrical configurations of the branching point, will be able to be used in connection with the controlling of the central particle flow.

Besides, other advantageous configurations of the invention are disclosed in the dependent claims.

BRIEF SUMMARY OF DRAWING FIGURES

The invention will now be explained in more detail with reference to the example embodiment shown in the drawing, where

Fig. 1 shows a principle set-up of the flow system in a first embodiment according to the invention,

Fig. 2 shows a principle set-up of the flow system in a second embodiment according to the invention, while

Fig. 3 shows the principle involved in how a volume element can be controlled by use of electro-kinetic pumps according to the embodiment in Fig. 1.

DETAILED DESCRIPTION OF DISCLOSED EMBODIMENT

In Fig. 1 the reference Figure 1 indicates a liquid flow containing particles, which liquid flow is led into a central channel. The liquid flow is enveloped in a "carrier flow" 2 in the central channel, so that hydrodynamic focussing occurs, whereby the particles assume a very uniform movement pattern in the central channel.

At a suitable distance inside the channel an observation area 4 is arranged. In this area, the particles pass in an individual manner due to their so-called "focussing". Not-shown measuring equipment can be established in the observation area for providing measurements, which form the basis for the further passage of the particles through the system, cf. below.

After the observation area 4, the particles move further through the central channel and reach a merging area 31 where control liquids are led into the central channel from two connected channels 5 and 6. After the merging area, the channel is divided into two further channels 8 and 9 at the branching point 7.

It takes the particles a known time, τ, to move from 4 to 7. Within this period of time, τ, the control signals, which control the control liquids, are generated. The time, τ, is determined by the length of the channel and the rate of flow in this channel.

The particles from the liquid flow will now be introduced into the channels 8 or 9, depending on how much control liquid is introduced into the channels 5 and 6 from two reservoirs 10 and 20.

It should be noted that the control liquids could be other than the particle-containing liquid and the carrier flow, which provides degrees of freedom in optimising the electro-kinetic pumping.

The control liquid from the reservoirs 10 and 20 is pumped by means of a pump structure, which is based on an electro-kinetic effect, e.g. electro-osmosis.

In Fig. 1 the pump structure is shown as a capillary structure 12 between the reference Figures 11 and 13. The drawing shows identical structures on each side of the central channel and branching point 7, in that the additional structure is indicated by the reference Figures 22, 21 and 23, respectively.

With an electrical field applied over a part of the capillary structures between supply pieces 11 and 13 and 21 and 23, liquid is pumped from the reservoirs 10 and 20 in towards the central particle flow.

As will appear from Fig. 1, the merging area is electrically earthed at 13 and at 23, respectively. The whole of the channel system is hereby held at a safe potential, and the relatively high potential, which is required for pumping, can be limited to the structures between 13 to 10 and 23 to 20, respectively.

The amount of liquid, which is pumped through the capillary structures, is controlled by changing the magnitude of the applied electrical field, which can be modulated temporally. A typical field strength is of 200 volts/cm, and the overall potential measured between 10 and 23 can be up to several kilovolts.

The high voltage supplies 14 and 24 are connected to electrical earth at 3 and 18, respectively.

In a typical set-up, a constant total amount of control liquid is pumped through the two capillary structures. It is hereby avoided that the pressure conditions around the introduction of the enveloped liquid flow are influenced by the sorting function. In other words, an increase/reduction of the amount of liquid in the one channel will result in a corresponding reduction/increase of the amount of liquid in the other channel.

With many applications, the ratio between the control liquids can with advantage be arranged so that a changeover of the control liquids in the ratio of 20:80 can be brought about.

This means, for example, that when a field is applied in the upper capillary 12, 13, 14 structure which corresponds to 20% of the total control liquid from the one reservoir 10 being supplied to the upper capillary structure, in the lower capillary structure the remaining 80% will thus be pumped from the second reservoir 20 and vice versa.

Fig. 2 shows a second embodiment in which an electro-kinetic pump is connected after the branching point 7. In this embodiment, only one pump is shown, which is sufficient to give rise to a change in the flow pattern. When the flow in the channel 8 is increased with a contribution via the merging point 30, a greater part of the main flow will be forced over into the other channel 9. The central particle flow will hereby be changed over from channel 8 to channel 9.

Here it should be noted that if a pump effect is not initiated from the electro-kinetic pump, the particles will then flow in the channel 8, which is due to the adjustment of the hydrodynamic focussing in the central channel, so that the particles move along the one side of the central channel, which in the drawing is shown at the observation area with the reference Figure 4.

The pump structures can alternatively be realised as external components, which e.g. are connected to the remaining flow system via an HPLC hose, or by part components being integrated on a common substrate.

In Fig. 3, the reference Figure 15 indicates a volume element of the central liquid flow with hydrodynamically focussed particles at 16 in the observation area 4 in Fig. 1. As will be seen, the focussed particles lie symmetrically around the axis 17.

After the introduction of control liquid from each of the channels 5 and 6, lowermost in Fig. 3 it is shown how control liquid from the

channels 5 and 6 can displace the focussed particles to the right or left in the branching point 7.

To the left in Fig. 3, the ratio between control liquids in the channels 5,6 is thus shown as being 20:80, cf. reference Figures 18 and 19, and on the right-hand side as 80:20. In the two cases, the focussed particles will be led to the channels 8 and 9, respectively.

Moreover, it should be noted that by increasing the length of the capillary pump structure, a higher hydrostatic pressure is achieved at unchanged diameter of the capillary structure and with no change in the applied electrical field.

With retained length and retained electrical field, the flow will be increased with the cross-sectional area of the pump channel, while at the same time a higher electrical current will flow.

The structure can be made of glass or of polymer material or of another suitable composition of materials, which are known within the field of micro-mechanics.

The channels can possibly be surface treated or coated with a thin film, e.g. in order to improve the electro-kinetic pumping.

It should be noted that special constructions would find application around the focussing zone and the detection point 4.

In general, the electro-kinetic pumps, which are described in connection with the said structures, will be able to be replaced by other pump mechanisms, though with subsequent modification of the system's parameters.